β-CARBOLINE PHARMACEUTICAL COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This is the U.S. national phase application of International Application No. PCT/US00/11130, filed on Apr. 26, 2000, which claims the benefit of provisional patent application Ser. No. 60/146,924, filed Aug. 3, 1999.

FIELD OF THE INVENTION

This invention relates to the fields of pharmaceutical and organic chemistry involving β-carboline compounds which are useful in the treatment of the various medical indications where inhibition of type 5 cGMP-specific phosphodiesterase is desired. More particularly, β-carboline compounds are formulated in a manner providing uniform potency, and desirable stability and bioavailability characteristics.

BACKGROUND OF THE INVENTION

The biochemical, physiological, and clinical effects of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP-specific PDE) inhibitors suggest their utility in a variety of disease states in which modulation of smooth muscle, renal, hemostatic, inflammatory, and/or endocrine function is desired. Type 5 cGMP-specific phosphodiesterase (PDE5) is the major cGMP hydrolyzing enzyme in vascular smooth muscle, and its expression in penile corpus cavernosum has been reported (A. Taher et al., *J. Urol.*, 149, pp. 285A (1993)). Thus, PDE5 is an attractive target in the treatment of sexual dysfunction (K. J. Murray, *DN&P* 6(3), pp. 150–56 (1993)).

Daugan U.S. Pat. No. 5,859,006 discloses a class of β-carbolines, and pharmaceutical compositions thereof, which are useful in the treatment of conditions wherein inhibition of PDE5 is desired. Also, see PCT publication WO 97/03675 disclosing the use of such β-carbolines for the treatment of sexual dysfunction.

The poor solubility of many β-carbolines useful as PDE5 inhibitors has prompted the development of coprecipitate preparations, as disclosed in Butler U.S. Pat. No. 5,985,326. Briefly described, coprecipitates of β-carbolines with a polymer, e.g., hydroxypropyl methylcellulose phthalate, were prepared, then milled, mixed with excipients, and compressed into tablets for oral administration. However, studies revealed some difficulties in generating precisely reproducible lots of coprecipitate product, thereby making the use of coprecipitates less than ideal for pharmaceutical formulations.

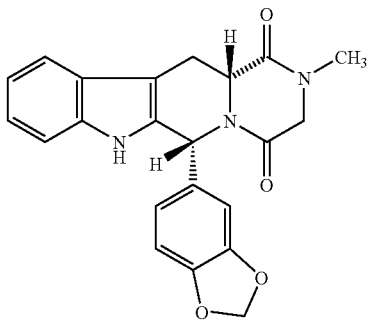
In addition, clinical studies involving administration of tablets containing such a coprecipitate preliminarily revealed that maximum blood concentration of the β-carboline is achieved in 3 to 4 hours, with the average time for onset of a therapeutic effect as yet not precisely determined. When used for the treatment of sexual dysfunction, such as male erectile dysfunction or female arousal disorder, a more rapid attainment of maximum blood concentration, along with a greater prospect for rapid onset of therapeutic effect, is desired by patients, who prefer more immediate effects.

Accordingly, there is a continuing need in the art for oral dosage forms of β-carbolines, and pharmaceutical compositions thereof, useful in the treatment of conditions where inhibition of PDE5 is beneficial.

SUMMARY OF THE INVENTION

This invention provides pharmaceutical formulations comprising a compound of structural formula (I):

(I)



named (6R-trans)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methylpyrazino-[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, and alternatively named (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl) pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione,

and pharmaceutically acceptable salts and solvates thereof, wherein the compound preferably is provided as a free drug,

in admixture with a diluent, a lubricant, a hydrophilic binder selected from the group consisting of a cellulose derivative, povidone, and a mixture thereof, a disintegrant selected from the group consisting of crospovidone, croscarmellose sodium, and a mixture thereof, and, optionally, microcrystalline cellulose and/or a wetting agent. Optionally, the formulation additionally comprises a second diluent.

A most preferred pharmaceutical formulation of the present invention comprises: (a) about 1 to about 5, and more preferably about 2 to about 4, weight percent of the compound of structural formula (I), provided as free drug; (b) about 50 to about 85 weight percent, and preferably about 50 to about 75 percent, lactose; (c) about 0.25 to about 2 weight percent magnesium stearate; (d) about 1 to about 5 weight percent hydroxypropylcellulose; (e) about 3 to about 15 weight percent croscarmellose sodium; (f) 0 to about 40 weight percent microcrystalline cellulose; and (g) 0 to about 5 weight percent sodium lauryl sulfate.

The present invention further relates to the use of such formulations for treatment of sexual dysfunction, e.g., male erectile dysfunction and female arousal disorder. The formulations can be administered orally as a compressed tablet or as dry, free-flowing particles encapsulated in a hard shell, for example, a gelatin shell.

DETAILED DESCRIPTION OF THE INVENTION

For purposes of the invention disclosed and claimed herein, the following terms and abbreviations have the following meanings.

The term "treatment" is defined to include preventing, lowering, stopping, or reversing the progression or severity of a condition or symptom being treated. As such, the present invention includes both medical therapeutic and/or prophylactic administration, as appropriate.